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Effects of a sustained extension on arterial growth and remodeling: a theoretical study

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Abstract

Three recent studies reveal that the unloaded length of a carotid artery increases significantly and rapidly in response to sustained increases in axial extension. Moreover, such lengthening involves an ''unprecedented'' increase in the rate of turnover of cells and matrix. Although current data are not sufficient for detailed biomechanical analyses, we present general numerical simulations that are consistent with the reported observations and support the hypothesis that rates of turnover correlate with the extent that stresses are perturbed from normal. In particular, a 3-D analysis of wall stress suggests that moderate (15%) increases in axial extension can increase the axial stress to a much greater extent than marked (50%) increases in blood pressure increase the circumferential stress. Furthermore, such increases in axial stress can occur without inducing significant gradients in stress within the wall. Consequently, we use a new, 2-D constrained mixture model to study evolving changes in the geometry, structure, and properties of carotid arteries in response to a sustained increase in axial extension. These simulations are qualitatively similar to the reports in the literature and support the notion that the stress-free lengths of individual constituents evolve during growth and remodeling.

Keywords: Arteries; Adaptation; Mixture theory; Stress–strain

1. Introduction

It has long been known that sustained perturbations in blood pressure or blood flow from normal values induce significant growth and remodeling (G&R) in arteries. For example, the arterial wall tends to thicken in response to sustained increases in blood pressure and the lumen tends to enlarge in response to sustained increases in blood flow (Langille, 1993). Moreover, it appears that these ''compensatory adaptations'' restore circumferential and wall shear stresses towards their original (homeostatic) values. It is not surprising, therefore, that it has recently been observed that sustained changes in axial extension can also induce significant G&R in arteries within short periods.

In particular, Jackson et al. (2002) reported an in vivo model wherein the left common carotid artery in the rabbit was subjected to an ~22% increase in axial strain while maintaining blood flow and blood pressure at near normal values. They found that the axial strain [defined as (in situ length−in vitro length)/(in vitro length)] decreased from 97 ± 2% to 72 ± 1% at 3 days, to 67 ± % at 7 days, to 55 ± 3% at 35 days, with ~ 62% being a normal value. In other words, the artery remodeled rapidly such that the axial strain (or stress) tended to re-normalize (i.e., the unloaded length increased over time). They reported that this G&R was due to dramatically increased rates of cellular proliferation (particularly at 3 days), and ''unprecedented'' increases in the synthesis of elastin and collagen, with cellular apoptosis and the upregulation of matrix metalloproteinases (e.g., MMP-2

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and MMP-9) playing significant roles. Finally, based on hemodynamic measurements and morphologic examinations of pressure-fixed cross-sections, they concluded that "changes in neither circumferential tensile stress nor shear stress can account for the rapid remodeling that normalized increases in axial strain."

The purpose of this paper, therefore, is two-fold. First, we present a 3-D analysis of stress for an acute extension of a common carotid artery to verify the suggestion of Jackson and colleagues that axial stretch induced G&R is controlled primarily by changes in axial stress. Second, motivated by the 3-D results, we use a new 2-D constrained mixture model for arterial G&R to show that a sustained extension can increase the unloaded length of an artery if new constituents are produced and organized relative to the new (stretched) state. Based on these findings, we agree that engineering arterial grafts via tissue-extension is a promising approach, but mathematical models coupled with increased data will aid in the design of such studies.

2. Methods

2.1. Analysis of stress

Methods for computing 3-D states of stress and strain in a multiaxially loaded artery, while accounting for residual stress, finite deformations, nonlinear anisotropic material behaviors and smooth muscle activation, are well known (cf. Humphrey, 2002, pp. 289–300). Briefly, we assume a quasi-static extension and inflation and account for the residual stress via Fung's opening angle. We also assume an exponential relation for the passive behavior (Chuong and Fung, 1986) and a polynomial expression for muscle contractility (Rachev and Hayashi, 1999), thus yielding an ordinary differential equation of (radial) equilibrium that is solved easily by numerical integration. Specific equations and parameter values are in Humphrey and Wilson (2003).

2.2. G&R model

Although we have formulated a 3-D constrained mixture theory for arterial growth and remodeling (Humphrey and Rajagopal, 2003), we have shown that a simpler 2-D theory can capture many of the salient characteristics (Gleason et al., 2004). Given that our 3-D analysis of an acute increase in axial extension reveals mild gradients in wall stress (see below), we use the 2-D G&R model herein. Briefly, similar to the usual 2-D equations of arterial mechanics, the requisite kinematic and constitutive equations for each constituent are:

$$\lambda_\theta^k = \frac{2\pi a^k}{2\pi A^k} \equiv \frac{a}{A^k}, \quad \lambda_z^k = \frac{\ell^k}{L^k} \equiv \frac{\ell}{L^k}, \tag{1}$$

$$\sigma_\theta^k = \hat{\sigma}_\theta^k(\lambda_\theta^k, \lambda_z^k), \quad \sigma_z^k = \hat{\sigma}_z^k(\lambda_\theta^k, \lambda_z^k), \tag{2}$$

where the superscript k denotes an individual constituent as well as its natural configuration (discussed below). Moreover, λ_i^k are the mean stretch ratios and σ_i^k the mean Cauchy stresses, with $i = \theta$ or z denoting circumferential and axial directions, respectively; a, ℓ, and h are the inner radius, axial length, and wall thickness in the deformed configuration whereas A, L, and H are values in a traction-free reference configuration; $a^k \equiv a$ and $\ell^k \equiv \ell$ by definition in a constrained mixture even though the individual natural configurations need not equal (i.e., $A^k \neq A, L^k \neq L$). Assuming a rule-of-mixtures relation for the stress response (Gleason et al., 2004), which admits different rates of turnover and different material behaviors for the primary structurally-important constituents within the wall, the total (mixture) stress is

$$\sigma_i(s) = \sum \phi^k(s)\hat{\sigma}_i^k(\lambda_\theta^k(s), \lambda_z^k(s)) \tag{3}$$

at any G&R times s, where $\phi^k(s)$ denotes an evolving mass fraction. Overall equilibrium in 2-D (Humphrey and Delange, 2004, pp. 118–128), combined with the constitutive and kinematic relations, thus yields the primary governing equations:

$$\frac{P(s)a(s)}{h(s)} = \sigma_\theta(s) = \sum \phi^k(s)\hat{\sigma}_\theta^k\left(\frac{a(s)}{A^k(s_p)}, \frac{\ell(s)}{L^k(s_p)}\right), \tag{4}$$

$$\frac{f(s)}{\pi h(s)(2a(s) + h(s))} = \sigma_z(s) = \sum \phi^k(s)\hat{\sigma}_z^k\left(\frac{a(s)}{A^k(s_p)}, \frac{\ell(s)}{L^k(s_p)}\right), \tag{5}$$

where P is the transmural pressure and f the applied axial load, each at any G&R time s. Note, too, that the natural configurations may evolve separately, where s_p denotes the time of production of a particular constituent.

For simplicity, and consistent with most experiments reported thus far, we restrict our attention to a single step change in extension. Hence, there will be two primary sets of natural configurations, original (o) and new (n). By original, we mean the homeostatic configuration associated with normalcy in maturity; by new, that associated with the extended configuration in which new constituents are produced and original constituents are removed. Assuming the dominant structurally-important constituents to be elastin (e), collagen (c), and smooth muscle (m), Eq. (3) reduces to:

$$\begin{aligned}\sigma_i(s) = {} & \phi^{\mathrm{oe}}(s)\hat{\sigma}_i^{\mathrm{oe}}(s) + \phi^{\mathrm{oc}}(s)\hat{\sigma}_i^{\mathrm{oc}}(s) + \phi^{\mathrm{om}}(s)\hat{\sigma}_i^{\mathrm{nm}}(s) \\ & + \phi^{\mathrm{ne}}(s)\hat{\sigma}_i^{\mathrm{ne}}(s) + \phi^{\mathrm{nc}}(s)\hat{\sigma}_i^{\mathrm{nc}}(s) + \phi^{\mathrm{om}}(s)\hat{\sigma}_i^{\mathrm{nm}}(s).\end{aligned} \tag{6}$$

Specific functional forms for the individual stress responses and specific values of the material parameters